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PRINCIPAL INVESTIGATOR: William H. Slattery, III, M.D.

CONTRACTING ORGANIZATION: House Ear Institute
Los Angeles, California 90057

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6. AUTHOR(S) :
William H. Slattery, III, M.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
House Ear Institute
Los Angeles, California 90057

e-mail:
wslattery@hei.org

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13. ABSTRACT ***(Maximum 200 Words)***

Neurofibromatosis 2 (NF2) is an autosomal disorder characterized by the development of multiple tumors within the brain and spinal canal. The purpose of the study is to define the growth rates and clinical course of tumors associated with NF2-affected individuals. An international consortium of clinical centers and expertise in NF2 will be developed, further expanding the infrastructure developed in the "Natural History of Vestibular Schwannomas in NF2" US Army grant. We will standardize the volumetric analysis of intracranial and spinal tumors, assess the patients' audiological, neurological, and ophthalmological functioning, and analyze molecular and clinical features of the disease over the course of 3 years.

Currently, 61 subjects are enrolled in the study. Of the subjects that have been scheduled for exams, 85% of GY Year 1 audiological, 100% of cranial MRIs, 92% of spinal MRIs, 88% of neurological, 92% of ophthalmologic, 81% of SF-36 health surveys and 77% of physical functioning questionnaires have been completed. We have made good progress toward completion of the study's goals and anticipate few problems with the collection of 1 yearYear 2 follow-up data.

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Introduction

Neurofibromatosis 2 (NF2) is an autosomal dominant disorder characterized by the development of multiple nervous system tumors. All patients develop bilateral vestibular schwannomas that lead to deafness and death if untreated. Patients also tend to develop multiple meningiomas and spinal tumors, which result in significant motor and sensory deficits if left untreated. In the past decade, great strides have been made in terms of radiographic diagnosis, surgical approaches to these tumors, and understanding of the molecular biology of NF2. Unfortunately, similar advances in the understanding of the natural history of these tumors, fundamental to the evaluation of treatments, have not yet been made. The purpose of this study is to define the growth rates and clinical course of tumors associated with NF2. We seek to accomplish this goal through the following steps:
Develop an international consortium of clinical centers with expertise in NF2, further expanding the infrastructure developed in the Natural History of Vestibular Schwannomas in NF2 US Army grant. All patients will be evaluated at local centers with full neurological, ophthalmological, radiographical, and audiometric evaluations and the data will be sent to a centralized center to analyze the data.

2. Develop standardized volumetric analysis of intracranial and spinal tumors. Currently, we have standardized the volumetric analysis of tumors on the hearing and balance nerves. We will attempt to standardize the measurement of the other tumors associated with NF2.
3. Form an infrastructure for use in future clinical trials. All NF2 patients identified at clinical centers will be categorized as potential subjects for future clinical trials.
4. Examination of molecular and clinical features which may predict tumor behavior.

This study will lead to a better understanding of the natural history and clinical course of tumors associated with NF2. The knowledge will allow better recommendations regarding current treatment options. An understanding of the natural history is also fundamental to the determination of efficacy of future medical or surgical therapies. Finally, the framework of clinical centers, data management, and scientific expertise established during this project will form the core for future studies investigating other aspects of the natural history of NF2 and for therapeutic treatment trials in NF2.

Body

STATEMENT OF WORK
Natural History of NF2 Consortium

Task 1. *Standardize Clinical Data Collection for NF2 Patients.*

a. **Finalize proposed case record forms. (month 1) : Completed**
All case record forms were created, finalized, and sent to all participating investigational sites. A Manual of Procedures, with the case record forms, has been sent to all investigational sites. The Manual of Procedures details the exact protocol to be followed to obtain the specified measurements in tumor size, hearing, eye evaluation, and quality of life and physical functioning.

b. **Creation of Comprehensive Care database and tracking system (months 1-3). : Completed**
A coordinated system for collecting and transmitting study data was established.

As detailed in the Manual of Procedures, House Ear Institute (HEI) serves as the Statistical Analysis and Data Management/Coordinating Center for the project. Clinical Coordinators send all original data to HEI. A Central Tracking System was established at HEI to track each subject and assure the consistent inflow of data from each site.

Files for each subject have been created and kept in a locked cabinet. A computerized database has been created to house the study data. As forms are sent to HEI, the data are entered into the database.

c. **Assist in translation of quality of life questionnaire and Comprehensive Care case record forms into Japanese and German (1-4). : In Progress**
At the outset of the study, Japan was included as one of the investigational sites of the NF2 Consortium. However, since that time, Japan has withdrawn from participation and a new investigational site has been added in France. Questionnaires and case record forms were sent to both the France and Germany investigational sites. Creation of French forms is in process.

d. **Modify previous NF2 natural history consortium methods for data transfer to comply with extra requirements required for Comprehensive Care database (months 1-3). : Completed**
Study methods have been created to ensure transmittal of data to HEI. Clinical Coordinators from each study site are in charge of contacting patients, setting up appointments or receiving scheduling information from subjects, assisting with insurance authorizations, communicating facility name and contact information to the Project Manager at HEI and to Meera Gupta, WorldCare. The Clinical Coordinator also attends the subject's exams, ensures completeness of the exams, and fills out the MRI Examination Outcome form and Data Transmission CRFs.

The MRI Facility performs the cranial and spinal MRI exams according to protocol, fills out the MRI Data Acquisition CRFs and gives them to the Clinical Coordinator, and invoices the investigational site for the stipend for completing the CRF.

WorldCare receives notification of subject information, exam date, and facility from the Clinical Coordinator. WorldCare ensures that test data are sent from the MRI facility to WorldCare and are acceptable.

Original, completed CRFs are sent to HEI. Queries regarding incomplete or inconsistent information on CRFs are answered by the Clinical Coordinator and WorldCare.

HEI tracks and monitors data flow, logs, dates and notes facilities, notes if data are received by WorldCare, follows up with the status of data.

Task 2. Standardize Volumetric Analysis of Intracranial Tumors and Spinal Tumors.

a. **Development of standard operating procedure for digital analysis of MRIs (months 1-3). Completed**
A Manual of Procedures is complete for both the Clinical Coordinators and WorldCare. The manual contains information for the data flow, acquisition protocol, and data transfer of images. WorldCare guidelines were merged with the HEI Manual of Procedures and were distributed to the Clinical Coordinators and Investigators at each investigational site.

b. **Preparation of facilities at WorldCare, Inc. (month 1). Completed**
A private suite for the NF2 Natural History Consortium has been prepared at WorldCare, Inc. At this time, all equipment and methods of sending and receiving data have been used for the collection and analysis of patient data. Also, the filing system, logbooks, and patient database are established to accept and track the workflow of patient data. An additional worksite has been set up next to the initial worksite to facilitate the radiologist reading the scans. The additional worksite has resulted in saving considerable time when transferring between images.

c. **Perform test/retest data of other cranial tumors and spinal tumors to determine amount of change required to be considered a statistically significant difference (months 1-3). : In Progress**
Test/retest data has been collected for other cranial tumors, specifically meningiomas. Acquisition and analysis of test/retest data for spinal tumors is in process.

d. **Perform qualitative and quantitative analysis of MRIs (months 4-33). : In Progress**
Of the 61 patients enrolled in the study, 26 patients have reached a timepoint in their clinical care regimen where baseline data can be collected. All 26 (100%) of these patients have had their Year 1 Cranial MRI exams and 24 (92%) have had their Spinal MRI exams. WC has scanned, analyzed, and sent HEI completed 15 (58%) of these Cranial MRI CRFs and 15 (63%) of these Spinal MRI CRFs. Additionally, the radiologist in charge of reading the MRIs indicates whether the MRI scans and corresponding data are acceptable to include in data analysis. Case record forms are checked to ensure accuracy of the data. Data cleaning is an ongoing process as data is received at HEI, entailing the checking of irregular data values, data editing, corrections and updating.

e. **Collection of yearly MRI data (months 1-35). : In Progress**
No patients have reached the time point for their Year 2 Follow-up exams.

Task 3. Prepare International Consortium of Clinical NF2 Centers.

a. **Modify previous NF2 natural history database for additional requirements of this study. : Completed**
The NF2 Natural History Database has been modified to include data for visual tests, quality of life and physical functioning questionnaires as well as modifications to CRFs for patient medical history, MRI, audiology, neurological, and molecular biology exams.

b. **Obtain local IRB approval (months 1-2). : Completed**
All nine study sites have received local IRB approval.

c. Obtain Army IRB approval and single project assurance approval (months 2-18). : In Progress

Of the nine sites that are participating in the study, all but one of the domestic sites and 2 of the foreign sites have received Army IRB approval and single project assurance.

SITE	APPROVAL
House Ear Institute	11/01/01
University of Texas	3/25/02
Massachusetts General Hospital	9/23/02
Royal Victorian Eye and Ear Hospital	10/10/02
University of Ohio	10/20/02
Klinikum Nord Ochsenzoll	11/3/02

The three sites that are in the process of receiving approval are Hopital Beaujon in Paris, St. Mary's Hospital in England and Mt. Sinai Hospital in New York.

f. Train centers on study protocol (spine, quality of life, comprehensive care) (months 3-6). : Completed

A meeting was held for all Clinical Coordinators and Principal Investigators to review the study protocol. Study protocol and manual of procedures were distributed to each Co-Principal Investigator and Clinical Coordinator at each site. HEI maintains ongoing telephone discussions with the Clinical Coordinators to facilitate the study and the timely collection of data.

d. Train centers in data transfer to Data Management Center (months 3-6). : Completed

All Clinical Centers have been given a manual of procedures informing them of the protocol for data transfer to the Data Management Center at HEI. Clinical Coordinators are responsible for sending all original, completed CRFs for audiology, neurological, and ophthalmology exams and medical history, SF-36 quality of life and physical functioning interview to the Project Manager at HEI. Original, completed MRI CRFs are sent to HEI by WorldCare.

Task 4. Subject Recruitment and Data Collection (months 3-30).

a. Enroll previous Natural History of Vestibular Schwannoma in NF2 patients in current study. : Completed

Some patients elected not to enroll in the new study and some patients were dropped by the local centers as they were non-compliant with the first study. The following patients have been enrolled:

Table 1: Patient Enrollment

Patient Collection Center	Location	Patients Enrolled From Previous Study	New Patients Enrolled	Total Patients Enrolled
House Ear Institute	Los Angeles, CA	19	15	**34**
Massachusetts General Hospital	Boston, MA	8	2	**10**
St. Mary's Hospital	Manchester, UK	NA	NA	**NA**
Klinikum Nord Ochsenzoll	Hamburg, Germany	11	0	**11**
Mt. Sinai Medical Center	New York, NY	NA	NA	**NA**
University of Texas, Houston	Houston, TX	0	1	**1**
Royal Victorian Eye and Ear Hospital	Melbourne, Australia	4	0	**4**
Ohio State University Hospital	Columbus, OH	1	0	**1**
Hopital Beaujon	Paris, France	NA	NA	**NA**
Total Patients Enrolled		**43**	**18**	**61**

NA – Sites that have not yet received IRB approval.

b. Individual centers identify potential patients to replace patients who dropped out. : In Progress

Clinical Coordinators at each investigational site screen their patient population and identify potential subjects for the Natural History of NF2 Consortium study.

c. New patients will complete baseline audiometric, MRI, neurological, ophthalmologic exams, SF-36 and physical functioning questionnaires and provide blood and tumor samples. : In Progress

Clinical Coordinators are responsible for ensuring patients complete Year 1 exams. Although a subject may have completed an exam, it is not considered complete until the original copy is received at HEI and entered into the database. Of the 61 enrolled patients, 26 patients have reached a timepoint in the course of their clinical care to have baseline exams conducted. Twenty-two (85%) Year 1 audiology exams have been completed and 19 (86%) of these have been received at HEI. Twenty-six (100%) of enrolled patients have had their Year 1 Cranial MRI exam and 15 (58%) of these have been received at HEI. Twenty-four (92%) have had their Spinal MRI exams and 15 (63%) have been received. Twenty-three (88%) patients have had their neurological exams and 19 (83%) have been received. Twenty-four patients (92%) had their ophthalmologic exams 18 (75%) have been received. Twenty-five (96%) SF-36 questionnaires have been sent to patients and 21 (84%) have been received. Twenty-five (96%) physical functioning questionnaires have been sent to patients and 20 (80%) have been received. Forty patients from the previous NF2 Natural History Study are now enrolled in the current study. These patients have all provided blood and tumor samples and analysis has been completed. Blood and tumor samples from the remaining patients still need to be collected.

d. All enrolled patients will be seen for yearly examinations.

HEI is in contact with the Clinical Coordinator from each site, providing information on upcoming follow-up exams to be scheduled. However, according to enrollment schedules, patients have not yet reached the 1-year follow-up time.

Task 5. Interim Analysis (months 12-18).

a. Interim statistical analysis and data obtained from initial audiometric, MRI studies, and clinical evaluations will be performed. : In Progress

Preliminary data analysis has begun. Currently, we are in the process of cleaning the data. Each patient is reviewed individually to clearly identify the start point and endpoint of any analysis.

Each tumor (either spinal, vestibular schwannoma (VS) or meningioma) is the unit of analysis with the start point being the date of each Year 1 exam and the endpoint being either the date of the first VS treatment or date of last follow-up if no treatment was performed.

Task 6. Final Analysis and Report Writing (months 30-36).

a. **Final analysis of data will be performed. : Pending**
Final analysis of the data will be performed when all CRFs have been received and all data have been entered into the database.

b. **Final report and initial manuscripts will be prepared. : Pending**
After all data has been entered into the database and all CRFs logged into our tracking system, a final report will be prepared, detailing the completion of all goals established at the outset of the study. Manuscripts on data obtained from the study will cover MRI exam methodology, vestibular schwannoma growth, growth of other NF2 tumors, audiological changes over time, neurological changes over time, quality of life in NF2 patients and visual characteristics of patients.

Key Research Accomplishments

- Development of an international consortium of clinical centers with expertise in NF2.
- Establishment of standardized study protocol for multi-institutional, multi-national natural history study.
- Development of NF2 specific database which includes clinical, radiographical, audiometrical, ophthalmologic, quality of life, and molecular biology/genetic information.
- Development of standard operating procedure for digital analysis of MRIs utilizing information from a variety of MRI machines from different manufacturers.

Reportable Outcomes

- Steering Committee Meeting, June 4, 2002:
  Interim data on the progress of this study were reported. The data collection process and direction of future data analyses were discussed by all Co-Principal Investigators.
- American Academy of Otolaryngology Head & Neck Surgery Meeting, September 22-25, 2002:
  Volumetric Analysis of Vestibular Schwannomas in NF2, submitted January 2003.
- "Short-term Hearing Changes After Diagnosis in Neurofibromatosis (NF2)", paper in revision.
- "MRI Scanner Reliability for Measuring Changes in Vestibular Schwannoma Size", revised paper submitted December, 2002.

Conclusions

The infrastructure necessary for this project to be successful has been assembled. A consortium of nine international sites with clinical expertise in NF2 has been established. All sites have received copies of standardized protocols for all data to be collected and a centralized database to store all information has been created. Subject enrollment had been difficult due to the delay in achieving Army approval of the informed consent forms for each institution. Much effort was given to ensuring that the MRI facilities used by study participants were compatible with WorldCare's systems. Despite these difficulties, 85% of Year 1 audiological, 100% of cranial MRIs, 92% of spinal MRIs, 88% of neurological, 92% of ophthalmologic, 81% of SF-36 and 79 % of physical functioning questionnaires have been completed.

References:

None